UDC 616.127-005.8-073.432.19-078:616.379-008.64
DOI 10.11603/1811-2471.2021.v.i4.12668

PECULIARITIES OF ALTERATIONS IN THE MYOCARDIAL STRUCTURE AND FUNCTION IN PATIENTS WITH ACUTE MYOCARDIAL INFARCTION AND TYPE 2 DIABETES TAKING INTO ACCOUNT FABP 4 AND CTRP 3

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SUMMARY. The study of inflammatory and anti-inflammatory processes of combined acute myocardial infarction (AMI) with type 2 diabetes mellitus (DM) is an urgent problem of modern medicine.

The aim – to determine the relationship between the fatty acid binding protein 4 (FABP 4), C1q/Tumor necrosis factor related protein 3 (CTRP 3) and echocardiographic parameters in patients with AMI in the presence of type 2 DM.

Material and Methods. The study involved examination of 134 patients with AMI. The first group consisted of 60 atients with AMI and the second group comprised 74 patients with AMI and type 2 DM. The control group included 20 healthy individuals. The content of FABP 4 and CTRP 3 was determined by enzyme-linked immunosorbent assay.

Results. Group 1 patients were shown to have a relationship between FABP 4 and end-diastolic size (EDS) (r=-0.458, p<0.01), end-systolic size (ESS) (r=-0.460, p<0.01), end-diastolic volume (EDV) (r=-0.452, p<0.01), left atrium (r=-0.487, p<0.01), left ventricular myocardial mass (LVMM) (r=-0.411, p<0.01), LVMM index (r=-0.419, p<0.01) and between CTRP 3 and EDS (r=0.469, p<0.01), EDV (r=0.425, p<0.01), stroke volume (r=0.407, p<0.05), the relative thickness of the posterior wall of the LV (RPWLVT) (r=-0.469, p<0.01). Group 2 patients were found to have a relationship between FABP 4 and ESS (r=-0.452, p<0.01), end-systolic volume (r=-0.482, p<0.01), LVMM (r=-0.424), p<0.01), LVMMI (r=-0.464, p<0.01), LV ejection fraction (EF) (r=0.402, p<0.01) and between CTRP 3 and EDS (r=0.402, p<0.01), EDV (r=0.424, p<0.01), LV EF (r=-0.465, p<0.05).

Conclusion. In Groups 1 and 2, echocardiographic parameters had reliably low inverse correlations with FABP 4 and low direct correlations with CTRP 3, except for RPWLVT and EF.

KEY WORDS: adipokines; echocardiographic indicators; myocardial infarction; diabetes.

Introduction. Diabetes mellitus (DM) is regarded as a trigger for cardiovascular disease (CVD). Sivolap V.D., Mikhailovskaya N.S. [1] found that DM significantly affects the structural and functional reorganization of the heart after myocardial infarction, which was confirmed by the relationship between carbohydrate metabolism and cardiohemodynamic parameters. According to Kravchun P.P. [2], type 2 DM is a potentiator of left ventricular (LV) myocardial remodeling in patients with myocardial infarction. Protein that binds fatty acids 4 (FABP 4) and C1q/TNF-related protein 3 (CTRP 3) are adipokines which affect carbohydrate and lipid metabolism and are associated with inflammatory processes in the development and course of CVD [3; 4].

FABP4 is mostly expressed in adipose tissue and macrophages. One of the mechanisms is inflammatory signaling pathways: kinase/nuclear factor κB complex (IKK-β/NF-kB) and c-Jun N-terminal protein kinase 1 (JNK1) [5]. These inflammatory signaling pathways are responsible for phosphorylating serine and threonine in substrate proteins by inhibiting signal transduction to insulin receptors. Increased release and transfer of NF-kB to the nucleus stimulates the expression of genes encoding proteins. They are involved in the development of insulin resistance. Dysfunction or loss of insulin receptors and inability to use glucose for cellular metabolism leads to hyperglycemia. IKK-β/NF-kB and JNK1 pathways may be activated by Toll-like receptors (TLRs), receptors of advanced glycation end products (RAGE) or by a non-receptor mechanism. It was determined that systolic and diastolic LV function is reduced in subjects with high serum FABP4 concentrations [6].

The effect of CTRP3 on glucose lowering is due to activation of the Akt signaling pathway and due to inhibition of hepatic gluconeogenic gene expression [7]. According to Ma Z.G. et al. [8], CTRP3 production occurs in the heart and CTRP3 is regulated through signaling pathways: Akt, AMPK, NF-kB. CTRP3 impairs abnormal myocardial reconstruction after AMI resulting from inhibition of myocardial fibrosis and improves survival and regeneration of ischemic cardiomyocytes [9]. However, the effect of FABP4 and CTRP3 on the myocardial structure and function in subjects with acute myocardial infarction (AMI) and type 2 DM remains insufficiently studied today.

The aim of the study was to assess the association between FABP4, CTRP3 and LV myocardial echocardiographic indices in patients with AMI and type 2 DM.

Materials and Methods. The study involved examination of 134 subjects with ST-segment elevation myocardial infarction (STEMI): 74 with DM and 60 without DM. The control group consisted of 20 healthy individuals. The study was performed between 01 September 2018 and 31 December 2020. The diagnosis of STEMI was established on the basis of clinical, instrumental and laboratory data, accord-

ing to the criteria proposed by the consensus of the European Society of Cardiology [10]. Type 2 DM was diagnosed and treated in compliance with the requirements of the American Diabetes Association and the European Association for the Study of Diabetes (2018, 2019) [11, 12]. Stenting of the affected coronary artery was performed in all the cases followed by medication, namely anticoagulant, acetylsalicylic acid, ticagrelor or clopidogrel, high dose of statin, nitrates, β-blocker (depending on heart rate), and angiotensin-converting enzyme inhibitor (for blood pressure correction), spironolactone or eplerenone (relative to the ejection fraction).

The inclusion criteria were patients with STEMI in the presence and absence of type 2 DM.

Exclusion criteria were type 1 DM, NSTEMI, Covid 19, autoimmune diseases, pituitary and hypothalamic diseases, thyroid disease, symptomatic hypertension, valvular heart disease, chronic heart failure IV FC to myocardial infarction, chronic obstructive pulmonary disease, chronic obstructive pulmonary disease, liver and kidney dysfunction, severe anemia, cancer.

The Ethics Commission of Kharkiv National Medical University (Minutes No.2 of 02 April 2018) approved the design of the study. All patients who participated in the study reviewed and signed a voluntary informed consent to participate in the study.

Within 1–2 days of observation the patients underwent serum collection and echocardiographic examination. Each part of the research was conducted in the biochemical department of the Central Research Laboratory of Kharkiv National Medical University of the Ministry of Health of Ukraine. Determination of FABP 4 and CTRP3 concentrations in patients' sera was performed by enzyme-linked immunosorbent assay using Human FABP 4 reagents from Elabscience Biotechnology, USA and Human CTRP 3 from Aviscera Bioscience Inc, Santa Clara, USA according to the kit instructions. Troponin I in blood serum was determined by enzyme-linked immunosorbent assay using "Troponin I" reagent manufactured by "Hema", Russia. Reference ranges were <0.05 ng/ml for men and women.

Doppler echocardiographic examination was performed according to the generally accepted method on Radmir ULTIMA Pro30ultrasound scanner. End-diastolic size (EDS), end-systolic size (ESS) of the LV, interventricular septal thickness (IVST), aortic size, size of the left atrium (LA), and posterior wall of the left ventricle (PWLVT) in diastole were determined. LV myocardial mass (LVMM), LVMM index (LVMMI=LVMM/body surface area (m2)) was calculated. LVH was established at an LVMMI value over 110 g/m2 for women and over 125 g/m2 for men. The study also involved calculation of the relative wall thickness (RWT) of the LV (RWT LV=(PWLVT+IVST)/EDSLV)) and LVMMI as well as determination of LV remodeling type. Concentric remodeling of the left ventricle was identified in RPWLVT≥0.45 and normal LVMMI [13, 14].

Statistical data were processed by licensed software package "IBM SPPS Statistics 27.0" (IBM Inc., USA). The hypothesis about the normality of the distribution of the studied indicators was tested using the Shapiro-Wilk test. Quantitative characteristics were presented as M±m (arithmetic mean±standard arithmetic mean error). Nominal variables were expressed as number and percentage. Paired comparison was performed using t test. χ^2 test was employed to compare nominal variables. Evaluation of the significance of the difference between the means of multiple comparisons for quantitative characteristics was performed with Bonferroni correction by one-way analysis of variance (ANOVA). Pearson correlation coefficient (r) was used to assess the relationships of the parameters. The difference was considered significant at p<0.05.

Results. 8.33 % of women and 91.67 % of men were consisted Group 1. The mean age of Group 1 was 58.42±1.07 years. 31.08 % women and 68.92 % men were included Group 2. The mean age of Group 2 was 59.42±0.89 years. 40 % women and 60 % men were consisted Control group. The mean age of Control group was 54.7±1.92 years.

Table 1 shows the echocardiographic parameters in the study groups. Assessment of structural-geometric and functional parameters of the heart revealed that Group 2 patients underwent dilation the left heart chambers, which was confirmed by an increase in LV EDV by 41.37 % (p<0.001), LV EDS by 13.68 % (p<0.001), LV ESV by 2.98 (p<0.001), LV ESS by 50 % (p<0.001), LVMMI by 2.04 (p<0.001). At the same time SV decreased by 6.84 % (p<0.001), LV EF by 20.24 % (p<0.001), which indicates a violation of the pumping and contractile function of the left ventricle.

Patients with type 2 DM, as compared with patients without type 2 DM, had significantly higher LV ESV by 23.05 % (p=0.007), LA size by 14.79 % (p<0.001), LVMM by 16.81 % (p=0.007). EDS, EDV, ESS of the LV tended to increase and LV EF to decrease, but without statistical reliability (p<0.05).

The contents of markers of adipokine metabolism are given in Table 2. FABP 4 and CTRP 3 values in the groups are shown in Table 3. Patients with AMI in the absence of type 2 DM (Group 1) and the presence of type 2 DM (Group 2) were found to have an increase in FABP 4 by 1.94 and 2.1 in comparison with the control group. FABP 4 levels were not significantly different between Groups 1 and 2 (p>0.05). A probable decrease in the concentration of CTRP 3 by 30.65 % in Group 2 compared with the control group (p<0.001) was determined. In Group 2 there was a decrease in CTRP 3 by 16.98 % compared with Group 1 (p<0.001).

Table 1. Echocardiographic indicators

Indicator, units of measurement	Group 1	Group 2	Control group	Probability (p)		
EDS, cm	4.90±0.06	5.07±0.07	4.46±0.06		2	3
				1	>0.05	0.004
				2	-	<0.001
ESS, cm	3.58±0.08	3.78±0.09	2.52±0.07		2	3
				1	>0.05	<0.001
				2	-	<0.001
EDV, ml	117.8±3.42	129.35±4.24	91.5±2.93		2	3
				1	>0.05	0.003
				2		<0.001
ESV, ml	53.92±2.59	66.35±3.22	22.25±1.81		2	3
				1	0.007	<0.001
				2	-	<0.001
SV, ml	64.03±1.88	64.51±2.42	69.25±3.67		2	3
				1	>0.05	>0.05
				2	-	>0.05
EF, %	53.90±1.17	50.45±1.14	63.25±2.63		2	3
				1	>0.05	<0.001
				2	-	<0.001
IVST, cm	1.16±0.03	1.24±0.02	0.85±0.02		2	3
				1	>0.05	<0.001
				2	-	<0.001
PWLVT, cm	1.17±0.03	1.25±0.02	0.78±0.02		2	3
				1	>0.05	<0.001
				2	-	<0.001
LA, cm	3.38±0.07	3.88±0.08	3.29±0.02		2	3
				1	<0,001	>0.05
				2		0.001
Aorta, cm	3.11±0.06	3.19±0.05	3.24±0.05		2	3
				1	>0.05	>0.05
				2	-	>0.05
LVMM, g	264.61±9.65	309.10±11.31	130.61±6.77		2	3
				1	0.007	<0.001
				2	-	<0.001
LVMMI, g/m^2	144.36±5.14	151.56±5.43	74.21±3.73		2	3
				1	>0.05	<0.001
				2	-	<0.001
RPWLVT	0.48±0.01	0.49±0.009	0.37±0.01		2	3
				1	>0.05	<0.001
				2	-	<0.001
Hypokinesia	48 (80)	62 (83.78)	-	p>0.05		
Akinesia	12 (20)	12 (16.22)	-	p>0.05		

Table 2.Indicators of adipokine metabolism: FABP 4 and CTRP 3

Indicator, units of measurement	Group 1	Group 2	Control group	p		
FABP 4, ng / ml	9.76±0.27	10.53±0.23	5.02±0.43		2	3
				1	>0.05	<0.001
				2	-	<0.001
CTRP 3, ng / ml	272.31±7.36	226.06±6.06	325.97±9.44		2	3
				1	<0.001	<0.001
				2	-	<0.001

Table 3. Correlations between echocardiographic indicators and adipokines in patients with AMI with type 2 DM

Indicator	1	2	3	4	5	6	7	8	9
FABP-4	1	-0.471**	-0.073	-0.452**	-0.173	-0.482**	0.193	0.402**	-0.180
CTRP-3		1	0.402**	0.199	0.424**	0.150	-0.018	-0.465*	0.064
EDS			1	0.572**	0.864**	0.561**	0.679**	-0.130	0.151
ESS				1	0.802**	0.816**	0.253*	-0.538**	0.131
EDV					1	0.734**	0.684**	-0.249*	0.129
ESV						1	0.120	-0.570**	0.077
SV							1	0.345**	0.083
EF								1	-0.039
IVST									1
PWLVT									
LA									
Aorta									
LVMM									
LVMMI									
RPWLVT									

Continuation of table 3

Indicator	10	11	12	13	14	15
FABP-4	-0.118	-0.131	-0.027	-0.424**	-0.464**	0.245*
CTRP-3	-0.006	0.115	-0.165	-0.041	-0.095	0.066
EDS	0.250	0.117	0.185	0.494**	0.469**	-0.245*
ESS	0.249*	0.143	0.108	0.333**	0.320**	-0.035
EDV	0.243*	0.152	0.188	0.422**	0.395**	-0.167
ESV	0.240*	0.197	0.165	0.386**	0.307**	-0.134
SV	0.129	0.046	0.073	0.240*	0.266*	-0.148
EF	-0.041	-0.084	-0.059	-0.066	-0.048	-0.007
IVST	0.613**	0.215	0.238*	0.653**	0.636**	0.603**
PWLVT	1	0.323**	0.433**	0.745**	0.694**	0.610**
LA		1	0.214	0.388*	0.307**	0.083
Aorta			1	0.419**	0.305**	0.093
LVMM				1	0.934**	0.122
LVMMI					1	0.125
RPWLVT						1

Note: * - p<0.05, ** - p<0.01

Patients with AMI were shown to have a direct association between troponin I and FABP 4 (r=0.457, p=0.009) and reverse relationship with CTRP 3 (r=- 0.415, p=0.008).

In patients with AMI, an inversely low relationship was found between FABP 4, EDS (r=-0.458, p<0.01), ESS (r=-0.460, p<0.01), EDV (r=-0.452, p<0.01), LA (r=-0.487, p<0.01), LVMM (r=-0.411, p<0.01), LVMMI (r=-0.419, p<0.01) and direct low correlation between CTRP 3, EDS (r=0.469, p<0.01), EDV (r=0.425, p<0.01), SV (r=0.407, p<0.05), RPWLVT (r=-0.469, p<0.01).

In patients with AMI and type 2 DM, there was an inversely low relationship between FABP 4, ESS, ESV, LVMM, LVMMI, and a direct low relationship with LV EF. A direct low correlation was found between CTRP 3, EDS, EDV and inversely low relationship with LV EF (Table 3).

Results and Discussion. Obokata M. et al. [15] found that FABP4 levels increase in patients with AMI. According to Aleksandrova K. et al. [16] elevated levels of FABP4 may contribute to the risk of type 2 DM. Von Jeinsen B. et al. [17] noted a direct relationship between FABP4 content and troponin T. According to Zhang J. et al. [18] FABP4 is expressed in cardiomyocytes, and its overexpression exacerbates the hypertrophic response of the heart caused by pressure overload. Harada T. et al. [19] noted increased LVMMI and determined a direct relationship between FABP4 concentration and LVMMI, LA size

and LV stiffness. FABP4 deficiency has been shown to improve LV function [20].

According to Yi W. et al. [21] the lowest level of CTRP 3 was observed 3 days after the development of AMI, although the beginning of the decrease in CTRP 3 occurred as early as on day 1. The use of recombinant CTRP3 reduced the size and weight of the myocardium and did not lead to increased dilatation of the left heart cavities in AMI. Ma Z-G. et al. [8] showed that CTRP3 content was reduced in the presence of DM. Excessive expression of CTRP3 in cardiomyocytes reduced oxidative stress and inflammation, thereby reducing myocyte death and improving cardiac function. CTRP3 is able to activate AMP-activated protein kinase α and Akt protein kinase B.

According to our findings, patients with AMI and type 2 DM were shown to have a tendency to increase the concentration of FABP 4 and decrease the level of CTRP 3. Moreover, patients with AMI in the absence of type 2 DM, were shown to have an increase in the content of FABP 4 and a decrease in CTRP 3 on days 1–2 of follow-up. A direct correlation between troponin I and FABP4 and an inverse relationship between troponin I and CTRP 3 was found in all patients with AMI. In patients with AMI and type 2 DM, FABP4 and CTRP 3 were associated with increased myocardial mass, LV enlargement due to increased EDS, EDV, ESS, ESV, LVMM, LVMMI, and worsening of LV myocardial contractility with decreased LV EF. Thus, the imbalance of markers of adipokine metabolism enhanced aggravation of the myocardial structure and function in subjects with AMI in the presence and absence of comorbid pathology.

Conclusions. The tendency to increase the content of FABP 4 was observed in patients with AMI in the presence and absence of comorbidity. Significant probable decreases in CTRP 3 were found in patients with AMI and type 2 DM. Significant low negative correlation between FABP 4 and echocardiographic parameters and low positive correlation between CTRP 3 and echocardiographic parameters were registered in patients with AMI and type 2 DM.

Prospects for further research. We plan to study markers of energy and adipokine metabolism in patients with type 2 DM 3 months after myocardial infarction.

Funding. This study is part of the research work of Academician L. T. Malaya Department of Internal Medicine No.2 and Clinical Immunology and Allergology of Kharkiv National Medical University "Ischemic heart disease in polymorbidity: patogenetic aspects of development, flowing, diagnostic and improvement of treatment" No. 0118U000929, valid term 2017–2019 and "Prediction of the flowing, improvement of diagnosis and treatment of ischemic heart disease and arterial hypertension in patients with metabolic disorders" No. 0120U102025, valid term 2020–2022.

Conflict of interest. The authors declare that no conflicts exist.

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ОСОБЛИВОСТІ ЗМІН СТРУКТУРИ ТА ФУНКЦІЇ МІОКАРДА У ХВОРИХ ІЗ ГОСТРИМ ІНФАРКТОМ МІОКАРДА ТА ЦУКРОВИМ ДІАБЕТОМ 2-ГО ТИПУ З УРАХУВАННЯМ ВМІСТУ FABP 4 І CTRP 3

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РЕЗЮМЕ. Актуальною проблемою сучасної медицини є вивчення запальних і протизапальних процесів поєднаного перебігу гострого інфаркту міокарда (ГІМ) із цукровим діабетом (ЦД) 2-го типу.

Мета – визначити взаємозв'язок між білком, що зв'язує жирні кислоти 4 (FABP 4), C1q / Фактором некрозу пухлини асоційованим білком 3 (CTRP 3) та ехокардіографічними показниками у пацієнтів із ГІМ за наявності ЦД 2-го типу.

Матеріал і методи. Обстежено 134 пацієнти із ГІМ. Першу групу склали 60 пацієнтів з ГІМ, а другу групу – 74 пацієнти із ГІМ та ЦД 2-го типу. Контрольну групу склали 20 практично здорових осіб. Вміст FABP 4 і CTRP 3 визначали імуноферментним методом.

Результати. У групі 1 визначено взаємозв'язок між FABP 4 і кінцеводіастолічним розміром (КДР) (r=-0,458, p<0,01), кінцевосистолічним розміром (КСР) (r=-0,460, p<0,01), кінцеводіастолічним об'ємом (КДО) (r=-0,452, p<0,01), лівим передсердям (r=-0,487, p<0,01), масою міокарда лівого шлуночка (ММЛШ) (r=-0,411, p<0,01), індексом ММЛШ (r=-0,419, p<0,01) та між CTRP 3 і КДР (r=0,469, p<0,01), КДО (r=0,425, p<0,01), ударним об'ємом (r=0,407, p<0,05), відносною товщиною задньої стінки ЛШ (ВТЗСЛШ) (r=-0,469, p<0,01). У групі 2 виявлено взаємозв'язок між FABP 4 і КСР (r=-0,452, p<0,01), кінцево-систолічним об'ємом (r=-0,482, p<0,01), ММЛШ (r=-0,424, p<0,01), ІММЛШ (r=-0,464, p<0,01), фракцією викиду (ФВ) ЛШ (r=0,402, p<0,01) та між CTRP 3 і КДР (r=0,402, p<0,01), КДО (r=0,424, p<0,01), ФВ ЛШ (r=-0,465, p<0,05).

Висновок. У групах 1 та 2 ехокардіографічні показники мали вірогідно слабкі зворотні кореляційні зв'язки із FABP 4 та слабкі прямі взаємозв'язки із CTRP 3, окрім ВТЗСЛШ і ФВ.

КЛЮЧОВІ СЛОВА: адипокіни; ехокардіографічні показники; інфаркт міокарда; цукровий діабет.

Отримано 21.10.2021

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